Practitioner's Docket No. R00212US (#90568)

CHAPTER II

Preliminary Classification:
Proposed Class: 604
Subclass: 890.1

NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.' " M.P.E.P., § 601, 7th ed.

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/04757	7 JULY 1999	9 JULY 1998

TITLE OF INVENTION: TRANSDERMAL PLASTER CONTAINING AT LEAST ONE ACTIVE INGREDIENT WHICH INFLUENCES BLOOD SERUM LIPID LEVELS

APPLICANT(S): BERTHOLD, Achim

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231

ATTENTION: EO/US

CERTIFICATION UNDER 37 C.F.R. § 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date January 8, 2001, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL148507545US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Christine A. Kotran
(type or print name of person mailing paper)
Christine A. Kotran
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

****WARNING:*** *Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing—See 37 C.F.R. § 1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 U.S.C. § 371 otherwise the submission will be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).

I. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. § 371:

a. ☒ This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. ☒ The U.S. National Fee (35 U.S.C. § 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
☒*	TOTAL CLAIMS	14 −20=	---	× $18.00=	$ ---
	INDEPENDENT CLAIMS	2 −3=	---	× $78.00=	---
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	---
BASIC FEE**	☐ U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: ☐ and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(1) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 C.F.R. § 1.492(a)(4)) ..... $96.00 ☐ and the above requirements are not met (37 C.F.R. § 1.492(a)(1)) ..... $670.00 ☒ U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: ☐ has been paid (37 C.F.R. § 1.492(a)(2)) ..... $690.00 ☐ has not been paid (37 C.F.R. § 1.492(a)(3)) ..... $970.00 ☐ where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 C.F.R. § 1.492(a)(5)) ..... XXXXXX $840.00 $860.00				860.00
	Total of above Calculations				= 860.00
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (note 37 C.F.R. § 1.9, 1.27, 1.28)				− ---
	Subtotal				860.00
	Total National Fee				$ 860.00
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. § 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				---
TOTAL	Total Fees enclosed				$ 860.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. ☒ A check in the amount of $860.00 to cover the above fees is enclosed.

ii. ☐ Please charge Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

***WARNING:** *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. ☒ A copy of the International application as filed (35 U.S.C. § 371(c)(2)):

NOTE: Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment. "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.

a. ☒ is transmitted herewith.

b. ☐ is not required, as the application was filed with the United States Receiving Office.

c. ☐ has been transmitted

i. ☐ by the International Bureau.
Date of mailing of the application (from form PCT/1B/308): _____.

ii. ☐ by applicant on _____.
Date

4. ☒ A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):

a. ☒ is transmitted herewith.

b. ☐ is not required as the application was filed in English.

c. ☐ was previously transmitted by applicant on _____.
Date

d. ☐ will follow.

5. ☒ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. ☐ are transmitted herewith.

b. ☐ have been transmitted

i. ☐ by the International Bureau.
Date of mailing of the amendment (from form PCT/1B/308): _____.

ii. ☐ by applicant on (date) _____.
Date

c. ☒ have not been transmitted as

i. ☒ applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210.): 3 December 1999

ii. ☐ the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. § 371(c)(3)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the amendments were made in the English language.

c. ☒ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ A copy of the international examination report (PCT/IPEA/409)

☒ is transmitted herewith.

☐ is not required as the application was filed with the United States Receiving Office.

8. ☐ Annex(es) to the international preliminary examination report (There are none.)

a. ☐ is/are transmitted herewith.

b. ☐ is/are not required as the application was filed with the United States Receiving Office.

9. ☐ A translation of the annexes to the international preliminary examination report

a. ☐ is transmitted herewith.

b. ☐ is not required as the annexes are in the English language.

10. ☒ An oath or declaration of the inventor (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

a. ☐ was previously submitted by applicant on _____. Date

b. ☐ is submitted herewith, and such oath or declaration

i. ☐ is attached to the application.

ii. ☐ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. § 1.70.

c. ☒ will follow.

II. Other document(s) or information included:

11. ☒ An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):

a. ☒ is transmitted herewith.

b. ☐ has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____.

c. ☐ is not required, as the application was searched by the United States International Searching Authority.

d. ☐ will be transmitted promptly upon request.

e. ☐ has been submitted by applicant on _____. Date

12. ☐ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:

a. ☐ is transmitted herewith.

Also transmitted herewith is/are:

☐ Form PTO-1449 (PTO/SB/08A and 08B).

☐ Copies of citations listed.

b. ☐ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).

c. ☐ was previously submitted by applicant on _____. Date

13. ☐ An assignment document is transmitted herewith for recording.

A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

_____

_____

_____

09/743292

08JAN2001

14. ☒ Additional documents:

a. ☐ Copy of request (PCT/RO/101)

b. ☒ International Publication No. WO 00/02541

i. ☐ Specification, claims and drawing

ii. ☒ Front page only

c. ☒ Preliminary amendment (37 C.F.R. § 1.121)

d. ☒ Other

Notification of the Recording of a Change; Written Opinion and response thereto in German; PCT/IPEA/416 (transmittal for IPER)

15. ☐ The above checked items are being transmitted

a. ☒ before 30 months from any claimed priority date.

b. ☐ after 30 months.

16. ☐ Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____, namely:

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 08-2441

☒ 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

09/743292

08 JAN2001

☒ 37 C.F.R. § 1.492(b), (c) and (d) (presentation of extra claims).

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

☒ 37 C.F.R. § 1.17 (application processing fees)

☒ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a).

☐ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

☐ 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

Reg. No.: 24,603

Tel. No.: (216) 771-3800

Customer No.:

SIGNATURE OF PRACTITIONER

D. Peter Hochberg

(type or print name of practitioner)

D. Peter Hochberg Co., L.P.A.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Achim Berthold

Serial No. :

Filed : (Herewith)

Title : TRANSDERMAL PLASTER CONTAINING AT LEAST ONE ACTIVE INGREDIENT WHICH INFLUENCES BLOOD SERUM LIPID LEVELS

Attorney File : RO0212US (#90568)

Box PCT
Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

Prior to substantive examination of the above-identified application, please amend the application, without prejudice, as follows:

In the specification:

Page 1, in the center of the page after the title and before the first line of text (line 4), insert -- BACKGROUND OF THE INVENTION -- ; at the left-hand margin before the first line of text, insert -- Field of the Invention -- ; at the left-hand margin between lines 15 and 16, insert -- Description of the Prior Art -- .

Page 4,in the center of the page between lines 27 and 28, insert -- SUMMARY OF THE INVENTION -- .

Page 5, in the center of the page between lines 8 and 9, insert -- DESCRIPTION OF THE PREFERRED EMBODIMENT -- ; lines 9-10, delete "of the kind as mentioned in the introductory portion of Claim 1" and insert -- containing at least one active substance having an influence on the lipid blood levels of an organism -- .

Page 10, after the last line, insert the following paragraph:

-- The invention has been described with particular emphasis on the preferred embodiments, but variations and modifications within the spirit and scope of the invention may occur to those skilled in the art to which the invention pertains. --

In the Claims:

1. (Amended) Preparation containing at least one active substance having an influence on the lipid blood levels of an organism, [characterized in that it] wherein said preparation is present in the form of a transdermal therapeutic patch containing the active substance in a self-adhesive matrix layer which can be covered at the side facing away from the skin with an active substance-impermeable backing layer.

Claim 2, line 1, replace "characterized in that" with -- wherein -- ; line 2, replace "it" with -- it further -- .

Claim 3, line 1,delete "1 or";lines 1-2, replace "characterized in that" with --wherein-- .

Claim 4, line 1, replace "one or more of claims 1 to 3" with -- claim 2 -- ; line 2, replace "characterized in that" with -- wherein -- .

Claim 5, line 1, replace "one or more of claims 1 to 4" with -- Claim 2 -- ; line 2, replace "characterized in that" with -- wherein -- ; line 3, replace "lovastatin" with -- selected from the group consisting of lovastatin -- ; line 5, replace "or" with -- and -- .

Claim 6, line 1, replace "one or more of claims 1 to 5" with -- claim 1 -- ; line 2, replace "characterized in that" with -- wherein -- , replace "layer of the matrix" with -- matrix layer --.

Claim 7, line 1, replace "one or more of claims 1 to 6" with -- claim 1 -- ; line 2, replace "characterized in that" with -- wherein -- .

Claim 8, line 1, replace "one or more of claims 1 to 7" with -- claim 7 -- ; line 2, replace "characterized in that" with -- wherein -- .

Claim 9, line 1, replace "one or more of claims 1 to 8" with -- claim 7 -- ; line 2, replace "characterized in that" with -- wherein -- .

Claim 10, line 1, replace "one or more of claims 1 to 9" with -- claim 7 -- ; line 2, replace "characterized in that" with -- wherein -- .

Claim 11, line 1, replace "one or more of claims 1 to 10" with -- claim 7 -- ; line 2, replace "characterized in that" with -- wherein -- .

Claim 12, line 1, replace "one or more of claims 1 to 11" with -- claim 7 -- ; line 2, replace "characterized in that" with -- wherein -- .

Claim 13, line 1, replace "one or more of claims 1 to 12" with -- claim 7 -- ; line 2, replace "characterized in that" with -- wherein -- .

14. (Amended) The [use] treatment of increased plasma lipid levels, said treatment comprising the administration of [the] a preparation for producing a means for lowering increased plasma lipid levels, especially in the case of systemic lipid metabolism disturbances, so-called hyperlipoproteinemias, as vascular diseases such as cardiac infarction, as well as in the case of occlusive arterial disease[.], said preparation existing in the form of a transdermal therapeutic patch containing the active substance in a self-adhesive matrix layer which can be covered at the side facing away from the skin with an active substance-impermeable backing layer.

REMARKS

The foregoing amendments to the application are made to place it in conformance with U.S. patent practice and to delete multiple-dependencies in the claims, thus reducing the government filing fee. No new matter has been added to the application by this amendment.

Accordingly, prosecution on the merits hereof is respectfully requested.

Respectfully submitted,

By: _____
D. Peter Hochberg
Reg. No. 24,603

DPH/ KRV/ Enc.

D. Peter Hochberg Co., L.P.A.
The Baker Building - 6th Floor
1940 East 6th Street
Cleveland, Ohio 44114
(216) 771-3800

EXPRESS MAIL CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that the foregoing Preliminary Amendment and any document(s) referred to as attached hereto is being deposited with the United States Postal Service on the date indicated below in an envelope as "Express Mail Post Office to Addressee" service mailing Label Number EL148507545US addressed: Box PCT, Commissioner for Patents, Washington, D.C. 20231.

Date: 1/8/2001

Christine A. Kotran
Christine A. Kotran

Transdermal Plaster Containing at Least One Active Ingredient which Influences Blood Serum Lipid Levels

The invention relates to a preparation containing at least one active substance which has an influence on the levels of lipids in the blood of an organism.

This active substance is a member of a group of active substances which intervene in the lipid metabolism of the organism and which are used for treating diseases related thereto.

Said substances are preferably inhibitors of hydroxymethyl-glutaryl-CoA reductase (HMG-CoA reductase).

Systemic lipid metabolism disturbances, especially so-called hyperlipoproteinemias, are of great significance in the pathogenesis of arteriosclerotic vascular diseases and of their consequences, such as cardiac infarction, apoplectic insultus and occlusive arterial diseases. In the USA and Europe about 15 percent of adults have an increased risk of suffering cardiovascular incidents because of increased lipid levels in the blood. A sensible starting point for prophylaxis, therapy and the treatment of consequences consists in lowering increased plasma lipid levels.
Basis for any treatment of hyperlipoproteinemia is an appropriate diet. A normalization of weight, appropriate diet composition, a proportion of fat <30% of the total number of calories, a sufficient dietary fiber intake, and a reduced cholesterol intake, especially <300 mg per day, must be

ensured. Furthermore it is advisable to increase the intake of unsaturated - above all monounsaturated - fatty acids, since these improve the metabolisation of lipoproteins. If by dietary measures alone it is not possible to achieve a sufficient normalization of the lipid blood level and if this means a higher risk of arteriosclerosis, lipid-lowering medicaments are indicated in addition. By treatment with lipid-lowering medicaments a marked reduction of these diseases can be achieved. Current studies, e.g. LCAS - Lipoprotein and Coronary Arteriosclerosis Study; LIPID - Long-term Intervention with Pravastatin in Ischemic Disease; CARE - The Cholesterol and Recurrent Events Trial, were able to show that drug therapy for prevention of arteriosclerotic vascular diseases is effective even where the lipid blood levels prior to treatment are only slightly increased or even within the normal range.

Long-term success of bypass operations is often restricted by atherosclerosis in the bypasses. The progression of atherosclerosis can be reduced by consistent lowering of the blood LDL level. It was possible to show that post-operative treatment with lovastatin keeps bypasses open longer and thereby leads to an improved prognosis of bypass operations.

Lipid-lowering medicaments can be classified into substances lowering the triglyceride as well as the cholesterol blood levels, and substances which first of all lower the cholesterol blood level. Among the substances belonging to the first substance group are, for example, aryloxyalcane carboxylic acids, e.g. clofibrate, etofibrate, etofylline clofibrate, bezafibrate, fenofibrate, gemfibrozil, nicotinic

acid, nicotinyl alcohol and acipimox. Examples for substances influencing mainly the cholesterol blood level are: anion exchange resins such as colestyramine or colestipol; inhibitors of hydroxymethylglutaryl-CoA reductase, HMG-CoA reductase, inhibitors such as lovastatin, simvastatin, mevastatin, pravastatin, fluvastatin, cerivastatin or atorvastatin, probucol, dextrothyroxine and sitosterol.

These substances inhibit hydroxymethylglutaryl-CoA reductase - an early stage of cholesterol synthesis. These inhibitors are the most potent substances for treatment of hypercholesterolemia.

Commercial administration forms are currently tablets and capsules with a dosage of 5 to 40 mg. The active substances are administered either in their active form, i.e. as the sodium salt of the hydroxy acid (e.g. pravastatin) or as a prodrug, i.e. in their lactone form (e.g. lovastatin). After oral treatment, however, only about 30% of the dose applied are absorbed from the gastrointestinal tract. The active substance portion absorbed is then subject to a considerable first pass effect. Absolute bioavailability ranges from 10 to 30%. The average elimination half-time of the active substance form lies within the range of 1 - 2 hours; exception: atorvastatin with 14 h.

Preparations containing HMG-CoA reductase inhibitors and intended for topical application are prior art. Substances of this class can be employed for the therapy of skin diseases. Here, the HMG-CoA reductase inhibitors serve as anti-psoriatics, for example as anti-aging agents for the skin, or

for the treatment of acne. The active compound here is incorporated in a classical administration form such as gel, ointment or cream. A non-therapeutic use consists in employing the substance class described herein for raising the percutaneous absorption rate of substances which can normally only insufficiently be absorbed.

Descriptions of systems considering a transdermal application of this class of substances are more scarce.
US 5,629,014 describes a system suitable, inter alia, for controlled release of lovastatin to the skin or mucous membranes. The system comprises a microcellular polyester or polyether foam serving as active substance reservoir. Since this foam is not adhesive itself, an additional means is necessary for fixing the foam on the surface of application. This foam-like system turns out to be relatively thick and inflexible. Application by the patient is thus not very practicable since the system, being exposed because of its height, is prone to being removed unintentionally and does not yield to movements of the body.

A transdermal application of lipid-lowering agents, indicated as the overall group, is mentioned in DE 36 34 016 C2. This system is characterized in that the component responsible for adhesion is present separately from the non-adhesive active substance reservoir.

Starting from the above-mentioned prior art, the invention has the object of providing a preparation containing at least one active substance which has an influence on the lipid blood levels of an organism, by which preparation it is

possible to achieve a release of the therapeutically active substance which takes place at a constantly low rate over prolonged periods of time and which can be accurately dosed, and which preparation, in particular, guarantees absolute bioavailability of the substance while affording a user-friendly mode of application, and with the said preparation serving as active substance reservoir.

To achieve this object, in a preparation of the kind as mentioned in the introductory portion of Claim 1, it is proposed by the invention that the said preparation be present in the form of a transdermal therapeutic patch (TTS) containing the active substance in a self-adhesive matrix layer which on the side facing away from the skin can be covered with an active substance-impermeable backing layer.

The transdermal therapeutic application system according to the invention ensures an extremely efficient drug therapy wherein the release of the active substance remains virtually constant over a long period and can be accurately controlled, with the absolute bioavailability of the substance being significantly increased.

Further embodiments are provided according to the subclaims. In particular, the self-adhesive mass is characterized in that it contains at least one hydroxymethylglutaryl-CoA reductase-inhibiting active substance, and that it contains structural elements of a beta-hydroxycarboxylic acid (I) or a tetrahydro-4-hydroxy-6-oxo-2H-pyrans (ii). The active substance may be present in the form of its salt or in the form of an ester.

For the inventive patch, a self-adhesive mass based on polyacrylate, silicone, ethylene vinyl acetate, rubber, rubber-like synthetic homo-, co- or block polymers, or of a hot-melt adhesive or the like may be used.

Masses based on polyacrylate are characterized in that acrylic acid and/or alkyl acrylic acid, especially methacrylic acid or its derivatives, especially the alkyl esters, are used for their production. Among the alkyl esters of acrylic acid and/or methacrylic acid, those are preferred which have 1 to 18 carbon atoms in the alkyl residue, especially methyl, ethyl, n-butyl, isobutyl, pentyl, 2-ethylbutyl, n-hexyl, heptyl, n-octyl, isooctyl, 2-ethylhexyl, n-decyl, isodecyl, n-dodecyl and stearyl acrylate or methacrylate. Apart from these, further comonomers can participate in the structure of the polymer/copolymer. Examples are acrylic and/or methacrylic amide, hydroxyalkyl esters and polyalkylene glycol esters of acrylic and/or methacrylic acid, nitrogen-containing monomers of acrylic and/or methacrylic acid or the salts thereof, ethylene, vinyl acetate, vinyl propionate, vinyl butyrate, vinylpyrrolidone, vinyl chloride, vinyl toluene, acrylonitril or styrene.

Masses based on silicone are characterized in that they have a large free volume, a low gas transition temperature, high flexibility and high gas permeability, are biocompatible, have a low surface tension and good wettability, are thermostable as well as chemically inert, and have good tackiness, adhesion and cohesion. Typically, silicone-based

masses contain a polycondensate, comprising a low-viscous polydimethyl siloxane and a silicate resin, characterized by a three-dimensional network. To increase the so-called amine resistance, it is possible for the terminal hydroxyl group of the polydimethyl siloxane to be condensed with trimethyl siloxane.

Examples for rubber-like synthetic homo-, co- or block polymers which may be employed according to the invention are polyisobutylene, polyisoprene, polystyrene, styrene-butadiene-styrene copolymers, styrene-isoprene-styrene copolymers, styrene-ethylene/propylene-styrene copolymers, styrene-ethylene/butylene-styrene copolymers, polyvinyl ethers, polyurethane, polybutadiene, styrene-butadiene copolymers, styrene-isoprene copolymers or styrene-isoprene-butylene block copolymers.

Furthermore, a backing layer may be contained which is connected with the self-adhesive mass. This backing layer may be impermeable to the active substance and have occlusive character. Any materials may be used which are employed in common preparations. Examples for such materials are cellulose acetate, ethyl cellulose, polyethylene terephthalate, plasticized vinyl acetate-vinyl chloride copolymers, nylon, ethylene-vinyl acetate copolymer, plasticized polyvinyl chloride, polyurethane, polyvinylidene chloride, polypropylene, polyethylene, polyamide or aluminum.

The composition may further comprise: tackifiers, penetration enhancers, agents for alleviating skin irritations, metal ions such as aluminum or titanium, and for increasing

cohesion: plasticizers, paraffins, cyclic hydrocarbons or vegetable oils.

As agents increasing tack, colophony resins, polyterpene resins, petroleum resins, coumarone-indene resins, terpene phenol resins, hydrocarbon resins or liquid polybutene resins may be used.

Examples for agents enhancing the penetration of the active substance are: pyrrolidone derivatives, fatty acids, fatty alcohols, fatty acid esters, fatty ethers, paraffin derivatives, terpenes, ethylene glykol monoalkyl ethers, polyoxyethylene alkyl ethers, polyoxyethylene aryl ethers, polyoxyethylene alkyl esters, polyoxypropylene alkyl ethers, propylene glycol fatty acid derivatives, glycerol fatty acid esters, polysorbates, poloxamers, dialkyl sulfoxides, urea and urea derivatives, glycerol, native oils, laurocaprames, phospholipides, amides, amino acids, N,N-dimethyl formamide, N-methyl formamide, acetonides, calcium thioglycolate, propylene glycol, polyethylene glycol, alkyl sulfate, sodium lauryl sulfate, tetrahydrofurfuryl alcohol, N,N-diethyl-m-toluamide, anticholinergics, macrocyclic compounds or polar solvents such as isosorbitol and panthenol.

The preparation according to the present invention may also contain agents for alleviating skin irritations, such as bisabolol, chamomile oil, allantoin, glycerol or dipanthenol.

The invention will be explained in the following by means of examples:

EXAMPLE 1

626 g of a solution of a self-adhesive polymer based on silicone (e.g. BIO PSA X7-4301, 70%-wt. in n-heptane) and 48 g of 2-pyrrolidone (with lovastatin) were mixed and, with the aid of a doctor knife, applied as a film of 600 µm thickness onto a fluoropolymerized polyester film (e.g. Scotchpak® 1022). The moist film was dried for 30 minutes at 50 °C and subsequently laminated with a polyester film (e.g. Hostaphan RN 15). The weight per unit area of an adhesive film prepared in this manner was about 300 g/m². From the laminate, TTSs of the desired size were punched out by means of a suitable punch, and in vitro permeation through isolated cow udder skin was measured. The flow rate was on average 0.3 µg/cm²/h over a period of 72 hours.

EXAMPLE 2

459.2 g of a solution of a self-adhesive polymer based on silicone (e.g. BIO PSA X7-4301, 70%-wt. in n-heptane) and 6.6 g of ethyl oleate (with lovastatin) were mixed and, with the aid of a doctor knife, applied as a film of 600 µm thickness onto a fluoropolymerized polyester film (e.g. Scotchpak® 1022). The moist film was dried for 30 minutes at 50 °C and subsequently laminated with a polyester film (e.g. Hostaphan RN 15). The weight per unit area of an adhesive film prepared in this manner was about 300 g/m². From the laminate, TTSs of the desired size were punched out by means of a suitable punch, and in vitro permeation through isolated cow udder skin was measured. Over a period of 72 hours the

incorporated active substance diffused almost quantitatively through the cow udder skin.

EXAMPLE 3

85.34 g of a self-adhesive, carboxyl group-containing polyacrylate (e.g. Durotak 387-2052, 48.1%-wt. in a mixture of ethyl acetate, n-heptane, 2-propanol and ethanol), 85.34 g of a hydrophile acrylate adhesive mixture (e.g. Plastoid E 35 H, 60%-wt. in ethyl acetate), 12.5 g ethyl acetate as well as 8.4 g of 2-pyrrolidone (with lovastatin) were mixed and, with the aid of a doctor knife, applied as a film of 400 µm thickness to a siliconized polyester film (e.g. Hostaphan® RN100). The moist film was dried for 30 minutes at 50 °C and subsequently laminated with a polyester film (e.g. Hostaphan RN 15). The weight per unit area of an adhesive film prepared in this manner was about 130 g/m².

C L A I M S

1. Preparation containing at least one active substance having an influence on the lipid blood levels of an organism, characterized in that it is present in the form of a transdermal therapeutic patch containing the active substance in a self-adhesive matrix layer which can be covered at the side facing away from the skin with an active substance-impermeable backing layer.

2. Preparation according to claim 1, characterized in that it contains at least one active substance inhibiting hydroxymethylglutaryl-CoA reductase.

3. Preparation according to claim 1 or 2, characterized in that the active substance inhibiting hydroxymethylglutaryl-CoA reductase contains the structural features of a beta-hydroxcarboxylic acid or of a tetrahydro-4-hydroxy-6-oxo-2H-pyrans in its molecule.

4. Preparation according to one or more of claims 1 to 3, characterized in that the active substance inhibiting hydroxymethylglutaryl-CoA reductase is present in the form of a salt or in the form of an ester.

5. Preparation according to one or more of claims 1 to 4, characterized in that the active substance inhibiting hydroxymethylglutaryl-CoA reductase is lovastatin, simvastatin, mevastatin, pravastatin, fluvastatin, atorvastatin, eptastatin or cerivastatin.

6. Preparation according to one or more of claims 1 to 5, characterized in that the self-adhesive layer of the matrix contains at least one homo-, co- or block polymer.

7. Preparation according to one or more of claims 1 to 6, characterized in that the self-adhesive matrix layer is a mass based on polyacrylate, silicone, polyisobutylene, polyisoprene, polystyrene, ethylene vinyl acetate, rubber or similar synthetic homo-, co- or block polymers.

8. Preparation according to one or more of claims 1 to 7, characterized in that the self-adhesive mass is a hot-melt adhesive.

9. Preparation according to one or more of claims 1 to 8, characterized in that the self-adhesive mass contains at least one auxiliary substance enhancing the permeation of the active substance through the skin.

10. Preparation according to one or more of claims 1 to 9, characterized in that the self-adhesive mass contains an auxiliary substance which increases tack.

11. Preparation according to one or more of claims 1 to 10, characterized in that the self-adhesive mass contains at least one plasticizer.

12. Preparation according to one or more of claims 1 to 11, characterized in that the self-adhesive mass contains at least one auxiliary substance alleviating skin irritations.

13. Preparation according to one or more of claims 1 to 12, characterized in that the self-adhesive mass contains at least one substance having an influence on cohesion.

14. The use of the preparation for producing a means for lowering increased plasma lipid levels, especially in the case of systemic lipid metabolism disturbances, so-called hyperlipoproteinemias, and vascular diseases such as cardiac infarction, as well as in the case of occlusive arterial disease.

Attorney Docket No. RO0212US (#90568)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Achim Berthold
Serial No.	:	09/743,292
I.A. Filing Date	:	July 7, 1999
Title	:	TRANSDERMAL PLASTER CONTAINING AT LEAST ONE ACTIVE INGREDIENT WHICH INFLUENCES BLOOD SERUM LIPID LEVELS

Box PCT
Commissioner for Patents
Washington, D.C. 20231

STATEMENT

Dear Sir:

I, Katherine R. Vieyra, an attorney registered in the United States Patent and Trademark Office, declare that the application mailed to the Patent and Trademark Office on January 8, 2001 is the application which the inventor executed by signing the attached Combined Declaration and Power of Attorney.

Respectfully submitted,

By: _____
Katherine R. Vieyra
Reg. No. 47,155

Attachments

D. PETER HOCHBERG CO., L.P.A.
1940 East 6th Street, 6th Floor
Cleveland, Ohio 44114
(216) 771-3800

EXPRESS MAIL CERTIFICATE

I hereby certify that the paper(s) identified above, and any noted as being attached, is being deposited with the United States Postal Service as Express Mail Label Number EL148507899US , postage prepaid, on the date indicated below and addressed: Box PCT, Commissioner for Patents, Washington, DC 20231.

March 27, 2001
Date

_____
Katherine R. Vieyra
(Signature of Person Mailing Papers)

ABSTRACT

A preparation containing at least one active substance having an influence on the lipid blood levels of an organism is characterized in that it is present in the form of a transdermal therapeutic patch containing the active substance in a self-adhesive matrix layer which can be covered at the side facing away from the skin with an active substance-impermeable backing layer.

LTS 1998/0.12 US

Attorney Docket No. **RO0212US (#90568)**

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL,CONTINUATION OR CIP)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: (check one applicable item below)

( ) original
( ) design

NOTE: If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application do not check any of next two items and check appropriate one of last three items.

(X) national stage of PCT
( ) supplemental

NOTE: If one of the following 3 items apply then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR CIP.

( ) divisional
( ) continuation
( ) continuation-in-part (CIP)

INVENTORSHIP IDENTIFICATION

My residence, post office address and citizenship are as stated below next to my name, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

TRANSDERMAL PLASTER CONTAINING AT LEAST ONE ACTIVE INGREDIENT WHICH INFLUENCES BLOOD SERUM LIPID LEVELS

SPECIFICATION IDENTIFICATION

the specification of which: (complete (a), (b), or (c))

(a) ( ) is attached hereto.
(b) (X) was filed on as ( ) Serial No. or
(X) Express Mail No. EL148507545US on January 8, 2001, as Serial No. not yet known and was amended on (if applicable).

(c) (X) was described and claimed in PCT International Application No. **PCT/EP99/04757** filed on **July 7, 1999** and as amended under PCT Article 19 on (if any).

ACKNOWLEDGEMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations. Sec. 1.56(a).

( ) In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.97.

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) ( ) no such applications have been filed.
(e) (X) such applications have been filed as follows

NOTE: Where item (c) is entered above and the International Application which designated the U.S. claimed priority check item (e), enter the details below and make the priority claim.

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

COUNTRY	APPLICATION NO.	DATE OF FILING (month,day,year)	PRIORITY CLAIMED UNDER 37 USC 119
			( ) YES NO ( )
			( ) YES NO ( )
			( ) YES NO ( )

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

German Appln. 198 30 732.2 filed July 9, 1998
and
PCT Appln. PCT/EP99/04757 filed July 7, 1999

POWER OF ATTORNEY

As a named inventor, I hereby appoint D. Peter Hochberg, Reg. No. 24,603, Katherine R. Vieyra, Reg. No. 47,155, and William H. Holt, Reg. No. 20,766, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO:	DIRECT TELEPHONE CALLS TO: (Name and telephone number)
D. Peter Hochberg Co., L.P.A. 1940 East 6th Street - 6TH Floor Cleveland, Ohio 44114-2294	D. Peter Hochberg (216) 771-3800

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full name of **sole or first inventor: Achim Berthold**

Achim Berthold
Inventor's signature

27. Januar 2001 — Germany
Date — Country of Citizenship

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Full name of **second joint inventor**, if any:

Inventor's signature

Date Country of Citizenship

Residence

Post Office Address

CHECK PROPER BOX(ES) IF ANY OF THE FOLLOWING ADDED PAGE(S) FORM A PART OF THIS DECLARATION

( ) Signature for third and subsequent joint inventors. Number of pages added _____ .

( ) Signature by administrator(trix), executor(trix) or legal representative of deceased or incapacitated inventor. Number of pages added _____ .

( ) Signature for inventor who refuses to sign or cannot be reached by person authorized under 37 CFR 1.47. Number of pages added _____ .

***

( ) Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (CIP) application.

( ) Number of pages added _____ .

***

If no further pages form a part of this Declaration then end this Declaration with this page and check the following item.

(X) This declaration ends with this page.